REMARKS

The Office Action has rejected Claims 13-20 as defining subject matter which is allegedly rendered obvious by the teachings in an article by Furuta et al., Jpn. J. Cancer Chemother, 18(3), 393-402 (1991) (hereinafter "Furuta et al.").

Applicant has added claims which, when considered with the comments herein, places the present case in condition for allowance. Favorable action is respectfully requested.

Claims 21-27 have been added to the application. The subject matter therein is supported in the instant specification. For example, support for the subject matter of Claim 21 is found on page 2, lines 3-5, and page 3, lines 3-9 as well as original Claims 2 and 6 of the instant application. Support for Claim 22 is found on page 4, lines 10-14 of the instant application. Claims 23 and 24 are supported by original Claims 9 and 12, respectively, of the instant application. Claims 25 is supported by Fig. 1 and Examples 3,4 and 5 and original Claim 20. Claims 26 and 27 are supported by Examples 3,4,5 and 6 and Fig. 1 of the instant specification.

No new matter is added to the application.

The Office Action has rejected Claims 13-20 under 35 U.S.C. §103, in defining subject matter which is allegedly rendered obvious by Furata et al.

Furata et al. discloses, inter alia, a method of treating L1210 mouse leukemia using a combination of CPT-11 and the anthracycline antibiotic, doxorubicin.

The Office Action alleges that Furata et al. teaches a method of treating L1210 leukemia by administering CPT-11 and doxorubicin in combination, whereby the two drugs provide a synergistic effect. It concludes that it would be obvious to one skilled in the art that

this combination would be useful for treating solid tumors, and that such combination would exhibit a synergistric effect in the treatment of solid tumors.

However, the teachings in Furata et al. are limited to the treatment of L1210 leukemia, which, as one skilled in the art knows, is not a solid tumor. There is no teaching or suggestion therein that this combination would be useful for treating solid tumors, as claimed herein.

The Office Action minimizes this omission, asserting that one would apply the teachings of Furata et al. to any type of tumor. Applicant respectfully disagrees.

It is widely recognized in the art of tumor therapy that a treatment regimen that is successful against one type of tumor (e.g., leukemia) will not necessarily be successful against other types of tumors (e.g., solid tumors). For example, L.M. Van Putten teaches that "[i]t is possible that differences in cellular biochemistry may be responsible for explaining the difficulty of treating by means of chemotherapy the majority of solid tumors [as compared to leukemias]." See Abstract of L.M. Van Putten, "Recruitment, a double-edged sword in cancer chemotherapy", Bulletin du Cancer, 60(2): 140-141 (1973). Moreover, it has been noted that "solid tumors are less sensitive to apoptosis induced by anticancer drugs than leukemia and lymphomas." See Abstract of M. Kawada, "Development of a Selective Apoptosis Inducer of Solid Tumor Cells", Biotherapy, 12(6): 967-973 (1988). Copies of both of these references were provided as exhibits attached to the Amendment filed December 3, 2003.

Thus, even assuming for the sake of argument that one were to be motivated by Furuta et al. to apply the teachings of Furata et al. to other cancers, such as solid tumors, that person would have no reasonable expectation of success in treating solid tumors.

Rather, at most, one of skill in the art would see Furuta et al. as a mere invitation to attempt to treat solid tumors, not a reasonable expectation of success. In other words, any motivation that Furata et al. might provide would be a motivation to try, not a motivation to succeed. MPEP §2145 X.B. prohibits rejections under this theory. Indeed, it is only through the teachings of the present specification that one of ordinary skill in the art would gain a reasonable expectation of success in treating solid tumors with a therapeutic synergistic combination of camptothecin, or a camptothecin derivative, and a topoisomerase II inhibitor. However, applicant's own disclosure cannot provide the motivation or expectation of success necessary to render a claim obvious.

Therefore, because Furata et al. does not provide an adequate motivation or reasonable expectation of achieving the presently claimed invention, applicant respectfully submits that the presently claimed invention would not be obvious over Furuta et al.

Moreover, Furata et al. fails to teach the therapeutic synergy, as defined herein of the combination of campotothecin or campotothecin derivative and a topoisomerase II inhibitor. As explained on page 5 of the instant specification, a combination manifests a therapeutic synergy if it is therapeutically superior to one or other of the constitutents used at its optimum dose. This concept of therapeutic synergy is recited in the claims by use of the language "therapeutic synergy superior to each of the agents used alone at the optimum dosage".

Furata et al. did not evaluate the effect of the highest non-toxic dose of campotothecin or doxorubicin when administered as a single agent. Without such a determination it is not possible to determine the synergestic effect of the CPT-11 and doxorubicin combination or whether there is any "therapeutic synergy" described therein, as that term is defined in the claims.

When using one constitutent, such as CPT-11, one of ordinary skill in the art would expect that the best result would be achieved at the optimum dose (i.e., maximum tolerated dose or highest non-toxic does (HNTD)) for that constituent. However, it may be beneficial to a patient to use a smaller dose, possibly, for example, to limit side effects. A therapeutic synergistic combination allows a patient to receive a smaller dose (ie., less than the HNTD) of one or both constituents and provides results greater than would have been achieved with HNTD if one constituent had been used individually at the optimum dose thereof.

Applicant determined the HNTD for CPT-11 by intravenous (i.v.) and oral routes on various tumors.[1] See Specification, page 7, Table 1. The HNTD for CPT-11 per os (p.o.) was found to be 806.4 mg/kg (100.8 x 2 times per day x 4 days (6-9)) on PO3 tumors in B6D2F1 mice. See Specification, page 11, Table IV.

Additionally, applicant determined the HNTD for doxorubicin by i.v. on PO3 tumors to be 12.4 mg/kg (6.2 x 2 days of administration). See Specification, page 11, Table IV. This result is also consistent with what is known in the art. See, for example, Kolfschoten, G.M. et al., "Development of a Panel of 15 Human Ovarian Cancer Xenografts for Drug Screening and Determination of the Role of the Glutathione Detoxification System", Gynecologic Oncology, 76(3):362-8(2000). This reference reported the HNTD for doxorubicin by i.v. on human ovarian cancer to be 16 mg/kg (8 mg/kg x 2).

After determining the HNTD for each constituent, applicant combined the constituents to determine if there was a therapeutic synergistic effect, i.e, whether smaller doses of each individual constituent could be used in a composition and yet still achieve a result better than the HNTD of one of the individual constituents when used alone. Applicant demonstrated

such a therapeutic synergistic effect in several combinations reported in Table IV on page 11 of the specification.[1]

As stated hereabove, Furuta et al. does not teach HNTD dose for each individual constituent. In fact, Furuta, et al. determined the dose for each constituent not based upon the HNTD for each constituent, but instead used amounts that would produce a desired result, around 150 of the life prolonging rate T/C (%). See page 394, first paragraph. For example, Furuta et al. determined that a dose of 37.5 mg/kg (12.5 x days of administration on days 1,5, 9) of CPT-11 by i.p. administration in mice having L1210 (leukemia) tumors achieved that goal. See Table 3. (Applicant notes that this dose is $1/16^{th}$ of the reported HNTD for i.p. administration of CPT-11 in mice having colon cancer. See footnote 2.) Similarly, Furuta et al. determined that a dose of 18.75 mg/kg (6.25 x 3 days of administration on days 1,5,9) of doxorubicin i.p. administered in mice having L1210 (leukemia) tumors achieved that goal.[2]

The Office Action continues to argue that the data in Furuta et al. Table 3, "shows that the effect of two chemicals on the inoculated mice is greater than the effect of each of these chemicals individually" and refers to the example having 37.5 mg/kg CPT-11 (12.5 X 3 days of administration) producing 16.5 days of survival as exhibiting a synergistic effect. See Office Action dated October 20, 2004, at page 7. Applicant respectfully reiterates that the Office Action's statement is inconsistent with applicant's definition of therapeutic synergistic effect.

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[1]In the clinic, CPT-11 is generally administered by i.v. and oral routes. The HNTD for CPT-11 by i.v. was found to be 346.2 mg/kg in PO3 tumors on B6D2F1 mice. See Specification, page 7, Table 1. This HNTD is consistent with what is known in the art. See, for example, Chatelut, G.S., et al., Comparison of Intraperitoneal and Intravenous Administration of Irinotecan (CPT-1) in a Murine Peritoneal Colon 26 Model, Proc. Am., Assoc. Cancer Res., 38(3):305(1997). This reference reported the HNTD of CPT-11 by i.v. administration to be 300 mg/kg. Moreover, the HNTD for intraperitoneal (i.p.) administration of CPT-11 in mice having colon tumors was determined to be 600 mg/kg. See Chatelut abstract.

[2]The HNTD for i.p. administration of doxorubicin in mice having lung carcinoma was determined to be 15 mg/kg. See Schmid et al. "Differential Uptake of 1-(2-chloroethyl)-3-(trans-4-methylcyclohexl)-1-nitrosourea and Doxorubicin by Lewis Lung Carcinoma and Ridgway Osteoganic Sarcoma", Cancer-Res., 43(3): 976-9 (1983).

Moreover, applicant respectfully submits that the Office Action statement is not supported by all, and is contrary to some, of the data in Furuta et al. For ease of understanding, applicant refers to Table A below which is based on the data in Furuta et al. Moreover, this statement is contrary to the data in experiment 4 when it is compared to the data in experiment 3. In experiment 4, both chemicals are used and the days of survival are 11.7. In experiment 3, only doxorubicin is used and the days of survival are 11.7. The data in experiments 3 and 4 rebut the Office Action's statement that the effect of two chemicals is greater than the effect of each of these chemicals used individually. The data does not appear to suggest a therapeutic synergistic effect, as defined in the claims.

Table A. Compilation of Data from Four Experiments in Furuta et al.

Experiment	Total Dose of CPT-11 (12.5 mg/kg x 3 days of administration at days 1,5,9)	Total Dose of adriamycin (6.25 mg/kg x n days of administration)	Days of Survival
1	37.5	18.75, n=3	16.5
2	37.5	0	10.8
3	0	18.75, n=3	11.7
4	37.5	6.25, n=1	11.7

As further evidence that Furuta et al. does not teach a therapeutic synergistic combination, applicant directs the attention of the United States Patent & Trademark Office to the rate of survival of the mice in Furuta et al. Applicant notes that in experiments 2 and 3 in Table A above, the mice treated with one constituent survived about 12 days before they expired.

In experiment 1 in Table A, the example relied upon by the Examiner as evidencing a therapeutic synergistic effect, the mice survived about 5 days longer for a total of 17 days.

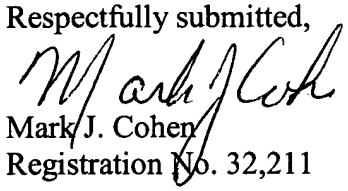
In comparison, in the examples provided in the present specification in Table IV, the mice treated with CPT-11 alone survived for at least 26 days. (The data is Table IV is not directed to days of survival as in Furuta et al., but is instead directed to the time in days for the tumors to reach 1000 mg. Therefore, presumably, the mice lived longer than is reported). The mice treated with doxorubicin alone survived for least 24 days. The mice that were treated with a therapeutic synergistic combination of CPT-11 and doxorubicin survived for at least 52 days. The rate of survival for mice treated with the therapeutic synergistic combination is almost double the rate of survival for the mice treated with the individual constituents alone, and more than three times the rate reported in Furuta et al. This result is unexpected in view of the teachings in Furuta et al.

Because Furuta et al. does not teach determining the HNTD of either CPT-11 or adriamycin alone, or finding a combination that provides a therapeutic synergistic effect that is superior to one of these compounds, Furuta et al. does not suggest that CPT-11 and doxorubicin exhibit a therapeutic synergistic effect, as required by the present claims and, thus, it fails to render the claimed invention obvious.

Thus, for the reasons stated, the rejection of the claims under 35 U.S.C. §103 is obviated, and withdrawal thereof is respectfully requested.

Accordingly, the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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